HEPATITIS

Peginterferon alfa-2a (40KD) plus ribavirin in chronic hepatitis C patients who failed previous interferon therapy

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Gut 2006;**55**:1631–1638. doi: 10.1136/gut.2005.083113

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Revised version received 7 April 2006
Accepted for publication 25 April 2006
Published online first 27 June 2006

Background: The management of patients with chronic hepatitis C who have relapsed or failed to respond to interferon based therapies is an important issue facing hepatologists.
Aims: We evaluated the efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in this population by conducting a multicentre open label study.
Patients: Data from adults with detectable serum hepatitis C virus (HCV) RNA who had not responded or had relapsed after previous conventional interferon or conventional interferon/ribavirin combination therapy were analysed.
Methods: Patients were retreated with peginterferon alfa-2a (40KD) 180 μg/week plus ribavirin 800 mg/day for 24 or 48 weeks at the investigators' discretion. The study was conceived before the optimal dose of ribavirin (1000/1200 mg/day) for patients with genotype 1 was known. The primary endpoint was sustained virological response (SVR), defined as undetectable HCV RNA (<50 IU/ml) after 24 weeks of follow up. The analysis was conducted by intention to treat.
Results: A total of 312 patients (212 non-responders, 100 relapsers) were included. Of these, 28 patients were treated for 24 weeks and 284 for 48 weeks. Baseline characteristics between non-responders and relapsers were similar although more non-responders had genotype 1 infection (87% *v* 69%). Overall SVR rates were 23% (48/212) for non-responders and 41% (41/100) for relapsers. When data were analysed by genotype, SVR rates were 24% (61/253) in genotype 1 and 47% (28/59) in genotype 2/3.
Conclusions: These results in a large patient cohort demonstrate that it is possible to cure a proportion of previous non-responders and relapsers by retreating with peginterferon alfa-2a (40KD) plus ribavirin.

Pegylated interferon in combination with ribavirin is the current treatment of choice for chronic hepatitis C,[1] producing sustained virological response (SVR) rates of up to 63% in treatment naïve patients.[2–4] Prior to the availability of pegylated interferons, the standard therapy for chronic hepatitis C was conventional interferon monotherapy or conventional interferon plus ribavirin, which produced SVR rates of 5–19% and 31–49%, respectively.[5–8] As such, a substantial proportion of patients had already been unsuccessfully treated with conventional interferon based regimens when the pegylated interferons were introduced. As chronic infection with the hepatitis C virus (HCV) may result in cirrhosis, liver failure, and hepatocellular carcinoma,[1 9] these patients remain at risk of developing progressive liver disease, and their retreatment is a focus of ongoing clinical investigation.

Patients who fail interferon therapy can be classified as non-responders (those failing to clear HCV from serum at any time point during treatment) and relapsers (those who clear HCV during treatment only to relapse either while on therapy ('breakthrough') or after completion of treatment). A different pattern of response is generally seen in these two groups, with retreatment being more effective among patients who have achieved a partial response to their previous treatment.[10] Using conventional interferon plus ribavirin, retreatment of patients who had previously failed conventional interferon monotherapy has produced SVR rates of up to 15%.[10–13] Given the increased SVR rates now obtained with pegylated interferon/ribavirin combination therapy among treatment naive patients, retreatment of prior non-responders and relapsers with this combination is an area of growing interest.

Recently, Shiffman *et al* reported an SVR rate of 18% using the combination of peginterferon alfa-2a (40KD) plus ribavirin in a large cohort of previous non-responders to conventional interferon mono- or combination therapy.[14] However, these results were obtained in the context of a randomised controlled clinical trial sponsored by the National Institutes of Health (the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis study; ''HALT-C''), and it is not known whether this response rate can be replicated in clinical practice. In another clinical trial, Krawitt and colleagues[15] reported overall response rates of 20% for prior non-responders and 55% for prior relapsers when retreated with peginterferon alfa-2b and ribavirin.

In order to assess the efficacy and safety of peginterferon alfa-2a (40KD) with or without ribavirin in patients who had failed previous therapy with non-pegylated interferons, we conducted an open label study designed to be representative of routine clinical practice.

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; SVR, sustained virological response; EVR, early virological response; BMI, body mass index; ITT, intent to treat; NPV, negative predictive value; PPV, positive predictive value

METHODS

This was an open label, non-controlled, multicentre study conducted at 18 Canadian centres, from April 2001 to June 2004, as part of a larger multinational trial (study BV16209). We recruited both treatment naive and previously treated patients; this paper presents the results from the Canadian cohort of previously treated patients. The study was designed and initiated before the optimal treatment regimens for HCV genotype 1 (48 weeks of treatment; ribavirin 1000/1200 mg/day) and genotypes 2/3 (24 weeks of treatment; ribavirin 800 mg/day) were determined.[3] The study protocol was approved by the institutional ethics committees at each site and was conducted according to the Declaration of Helsinki.[16] Written informed consent was obtained from each patient prior to starting treatment.

Patients

We recruited male and female outpatients aged ⩾18 years with serological evidence of chronic hepatitis C by an anti-HCV antibody test and quantifiable serum HCV RNA (>600 IU/ml; Cobas Amplicor HCV Monitor, v2.0, Roche Diagnostics, Basel, Switzerland). All patients were required to have a liver biopsy prior to starting treatment that showed findings consistent with a diagnosis of chronic hepatitis C infection. Patients with bridging fibrosis/cirrhosis (defined as F3 or F4 disease using the METAVIR scoring system) were not excluded but were required to have Child-Pugh grade A compensated liver disease. Patients with persistently ''normal'' alanine aminotransferase (ALT) activity could participate if they had a liver biopsy result consistent with a diagnosis of chronic hepatitis C and ⩾F2 liver disease.

Patients had to have failed ⩾12 weeks of previous therapy with either conventional interferon monotherapy or conventional interferon/ribavirin combination therapy. Previous treatment regimens included conventional interferon alfa-2a or -2b monotherapy or consensus interferon monotherapy, or combination therapy with interferon alfa-2b plus ribavirin. We excluded patients previously treated with pegylated interferon treatment regimens. Other exclusion criteria were: hepatic decompensation; haemoglobin <10 g/dl; neutrophils <1500 cells/ml; platelets <90 000 cells/ml; autoimmune disease; uncontrolled major psychiatric syndromes; or active substance abuse. Human immunodeficiency virus positive individuals, those with other liver diseases, or significant disease of other organs were also excluded.

Treatment

Patients were treated with one of three regimens:

(1) peginterferon alfa-2a (40KD) monotherapy for 48 weeks;
(2) combination therapy with peginterferon alfa-2a (40KD) plus ribavirin for 24 weeks; or
(3) combination therapy with peginterferon alfa-2a (40KD) plus ribavirin for 48 weeks.

All patients were followed for a further 24 weeks without treatment. The treatment algorithm was decided at the investigator's discretion. Peginterferon alfa-2a (40KD) (Pegasys, Roche, Basel Switzerland) was administered subcutaneously at a dose of 180 μg once weekly. Ribavirin (Copegus; Roche, Basel, Switzerland) was administered orally at a dose of 800 mg/day in divided doses (400 mg twice daily). The chosen ribavirin dose of 800 mg/day was reflective of clinical practice at that time. Doses of peginterferon alfa-2a (40KD) or ribavirin were adjusted for side effects according to the manufacturer's recommendations.

Assessments

Quantitative viral titres were obtained at weeks 0 and 12 (Cobas Amplicor HCV Monitor, v2.0; lower limit of detection 600 IU/ml) in all patients. A qualitative HCV RNA assay (Cobas Amplicor HCV Test, v2.0; lower limit of detection 50 IU/ml) was performed at week 12 only in those patients who had a low viral load at baseline (>600 IU/ml to <60 000 IU/ml). Qualitative HCV RNA results were obtained after 24 weeks of treatment free follow up (week 48 in the 24 week treatment group and week 72 in the 48 week treatment group). The primary efficacy endpoint was SVR, defined as undetectable HCV RNA (<50 IU/ml; Cobas Amplicor HCV Monitor, v2.0) 24 weeks after the last dose of study medication (week 48 in the 24 week group and week 72 in the 48 week group).

Laboratory parameters were monitored and recorded at regular intervals throughout the study period and a physical examination was conducted at the end of treatment. Adverse events and serious adverse events were recorded throughout the study and up to week 12 of the follow up period.

Early discontinuation of treatment

It was recommended that treatment be withdrawn in patients who did not achieve an early virological response (EVR) by week 12. EVR was defined as a decrease in viral titre of ⩾2-$\log_{10}$ compared with baseline or a negative HCV RNA (<50 IU/ml; Cobas Amplicor HCV Monitor, v2.0) result at week 12 of therapy. After discontinuation, patients who did not achieve EVR were assessed for safety 4–8 weeks after their last dose of study drug.

Statistical analysis

No formal sample size calculation was performed. Data were collected and analysed by the Syreon Corporation (British Columbia, Canada) on an intention to treat (ITT) basis. The ITT population was defined as all patients who received ⩾1 dose of study medication.

Data were analysed according to the patients' prior treatment outcome (non-responders *v* relapsers), HCV genotype (1 *v* 2/3), and previous treatment (conventional interferon monotherapy *v* conventional interferon combined with ribavirin). Non-response to previous therapy was defined as failure to achieve suppression of HCV RNA to below the limit of detection at any time point during treatment. Relapse during or after previous therapy was defined as reversion to an HCV RNA positive state after suppression of HCV RNA below the limit of detection while on therapy or during follow up. This definition of relapse also included patients with ''breakthrough'' quantifiable HCV RNA.

The analysis excluded patients infected with genotypes other than 1, 2, or 3 due to the small number of patients involved. As pegylated interferon monotherapy is no longer widely used in clinical practice, patients who received peginterferon alfa-2a (40KD) monotherapy (treatment group 1) were also excluded from the analysis. Patients for whom a post-therapy HCV RNA result was not available or who were otherwise lost to follow up were considered treatment failures.

Multivariate logistic regression models were used to determine significant predictors of SVR for the relapser and non-responder patient groups. Each model included parameters for genotype (1 *v* 2/3), age (years), race (Caucasian *v* other), sex, weight (kg), body mass index (BMI), METAVIR fibrosis score (F0, F1, F2 *v* F3, F4), and log of viral load (IU/ml).

Efficacy and safety data are presented using descriptive statistics. The positive predictive value (PPV) (that is, the probability of achieving an SVR among those patients who achieved an EVR at week 12) and the negative predictive

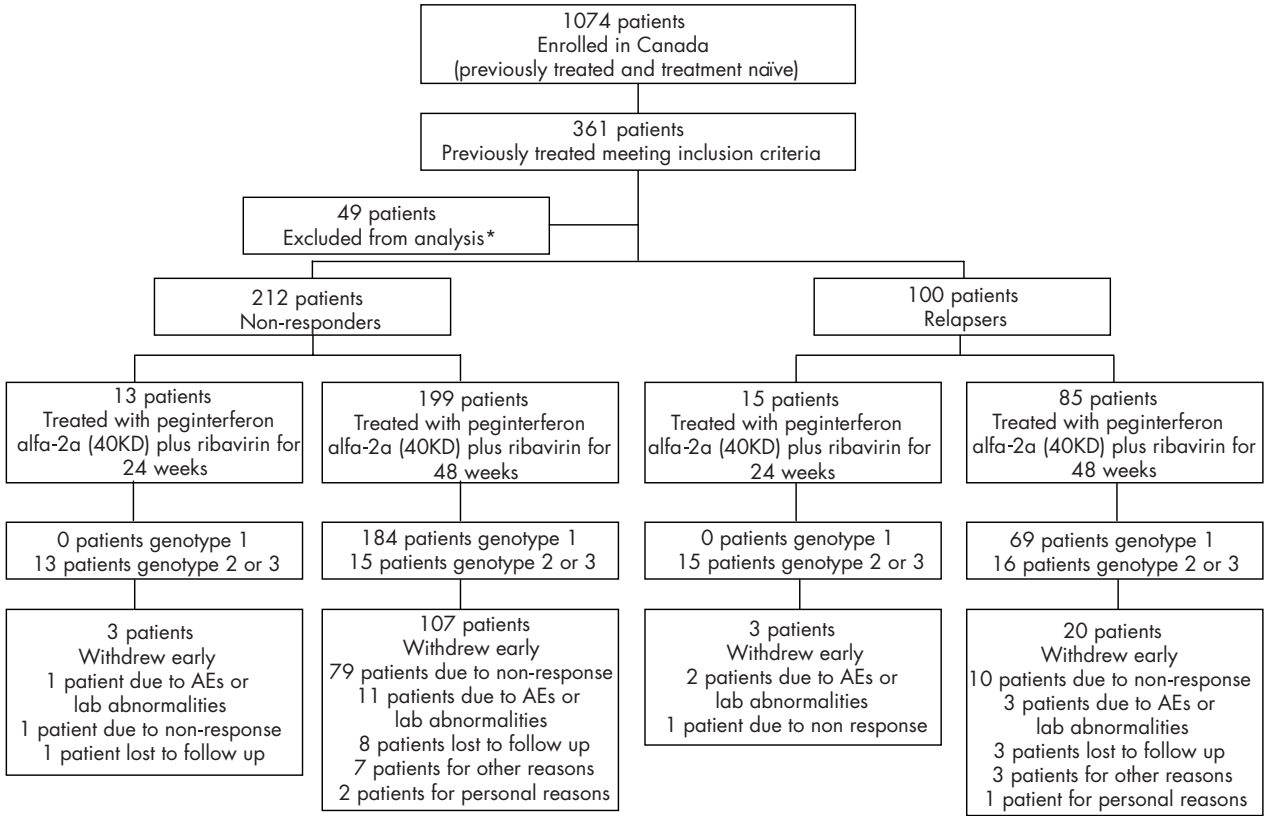

Figure 1 Patient disposition. AEs, adverse events. *Received hepatitis C virus (HCV) medications other than conventional/consensus interferon based therapies (n = 33); infected with HCV genotypes other than 1, 2, or 3 (n = 11); received peginterferon alfa-2a (40KD) monotherapy (n = 6); and one patient excluded due to two of these reasons.

value (NPV) (that is, the probability of not achieving an SVR for those patients who failed to achieve an EVR) were calculated.

RESULTS

Study population

Patient disposition is shown in fig 1. Information on the total number of patients screened but not included in the study was not recorded. Overall, 1074 Canadian patients (including treatment naive and previously treated patients) were enrolled. Of these, 361 previously treated patients met the study inclusion criteria. The results for the treatment naive population are reported elsewhere.[17] Forty nine of 361 previously treated patients were excluded from the analysis. This included 33 patients who had received prior unsuccessful therapy with HCV medications other than conventional interferon and 11 patients who were infected with HCV genotypes other than 1, 2, or 3. In addition, six patients who were retreated with pegylated interferon monotherapy (treatment group 1) were also excluded. One patient was excluded for two of the aforementioned reasons. Thus data from 312 non-responder/relapser patients retreated with peginterferon alfa-2a (40KD) plus ribavirin were available for analysis.

A total of 253 patients (81%) were infected with HCV genotype 1, and 59 (19%) were infected with either genotype 2 or 3. The majority of patients (n = 244; 78%) had been previously treated with conventional interferon/ribavirin combination therapy. Of these, 77 were relapsers and 167 were non-responders. Sixty eight patients (22%) had previously been treated with conventional interferon monotherapy, of whom 23 and 45 were prior relapsers and prior non-responders, respectively (table 1).

Most patients (n = 284; 91%) were retreated with peginterferon alfa-2a (40KD) plus ribavirin for 48 weeks; only 28 patients received 24 weeks of treatment. Table 1 shows patient demographics and baseline characteristics according to treatment regimen. In total, 280 patients (90%) were Caucasian. The 48 week treatment group contained a higher proportion of men (71% *v* 64%). More patients were infected with HCV genotype 1 in the non-responder group versus the relapser group (87% *v* 69%). All patients infected with HCV genotype 1 received 48 weeks of treatment. Of note, approximately one half of all patients (n = 154; 49%) were found to have histological evidence of bridging fibrosis (METAVIR F3) or cirrhosis (METAVIR F4) on liver biopsy. In total, 81 (26%) had a histological score of F4 while a further 73 (23%) had a score of F3.

Efficacy of peginterferon alfa-2a (40KD) plus ribavirin in the retreatment of patients with chronic hepatitis C

Table 2 provides a summary of efficacy data. A greater proportion of relapsers (84/100; 84%) achieved an EVR at week 12 compared with non-responders (123/212; 58%). EVR status was unknown in 12 patients.

In total, 48/212 previous non-responders (23%) and 41/100 (41%) relapsers achieved an SVR (table 2, fig 2). When data were analysed according to HCV genotype, an SVR was observed in 61/253 (24%) genotype 1 patients and in 28/59 (47%) genotype 2 or 3 patients.

Efficacy of peginterferon alfa-2a (40KD) plus ribavirin according to previous treatment

Conventional interferon monotherapy

The overall response rate was higher in relapsers compared with non-responders (fig 2). In total, 27% (12/45) of previous

Table 1 Patient demographics and baseline characteristics

	Peginterferon alfa-2a (40KD) + ribavirin		
	24 week (n = 28)	48 weeks (n = 284)	Total (n = 312)
Sex (n (%) male)	18/28 (64.3)	202/284 (71.1)	220/312 (70.5)
Mean age (y)			
Non-responders	45.1	47.3	47.2
Relapsers	48.3	47.1	47.3
Caucasian (n (%))			
Non-responders	11/13 (84.6)	178/199 (89.9)	189/312 (60.6)
Relapsers	15/15 (100)	76/85 (89.4)	91/312 (29.2)
Asian (n (%))			
Non-responders	1/13 (7.7)	13/199 (6.5)	14/312 (4.5)
Relapsers	0/15 (0)	7/85 (8.2)	7/312 (2.2)
Other race (n (%))			
Non-responders	1/13 (7.7)	8/199 (4.0)	9/312 (2.9)
Relapsers	0/15 (0)	2/85 (2.4)	2/312 (0.6)
Mean BMI (kg/m^2)			
Non-responders	24.7	27.7	27.5
Relapsers	27.1	27.3	27.3
HCV genotype (n (%))			
Non-responders			
1	0/13 (0.0)	184/199 (92.5)	184/312 (86.8)
2 or 3	13/13 (100.0)	15/199 (7.5)	28/312 (13.2)
Relapsers			
1	0/15 (0.0)	69/85 (81.2)	69/312 (69.0)
2 or 3	15/15 (100.0)	16/85 (18.8)	31/312 (31.0)
HCV viral load (IU/ml) (n (%))			
Non-responders			
>850 000	1/13 (7.7)	63/199 (31.7)	64/312 (30.2)
⩽850 000	12/13 (92.3)	136/199 (68.3)	148/312 (69.8)
Relapsers			
>850 000	6/15 (40.0)	34/85 (40.0)	40/312 (40.0)
⩽850 000	9/15 (60.0)	51/85 (60.0)	60/312 (60.0)
Bridging fibrosis (F3) (n (%))			
Non-responders	5/13 (38.5)	43/199 (21.6)	48/312 (15.4)
Relapsers	1/13 (7.7)	24/199 (12.1)	25/312 (8.0)
Cirrhosis (F4)			
Non-responders	2/15 (13.3)	56/85 (65.9)	58/312 (18.6)
Relapsers	7/15 (46.7)	16/85 (18.8)	23/312 (7.4)
Previous HCV therapy (n (%))			
Non-responders			
Monotherapy	5/13 (38.5)	40/199 (20.1)	45/312 (21.2)
Combination therapy	8/15 (61.5)	159/85 (79.9)	167/312 (78.8)
Relapsers			
Monotherapy	8/13 (53.3)	15/199 (17.7)	23/312 (23.0)
Combination therapy	7/15 (46.7)	70/85 (82.4)	77/312 (77.0)

BMI, body mass index; HCV, hepatitis C virus.
Monotherapy, interferon alfa-2b, interferon alfa-2a, interferon alfacon-1
Combination therapy, interferon alfa-2b plus ribavirin.

non-responders to conventional interferon monotherapy had an SVR. For patients infected with HCV genotype 1, 22% (8/36) had an SVR, and for patients with HCV genotype 2 or 3, the SVR rate was 44% (4/9).

In patients who had relapsed during prior interferon monotherapy, the overall percentage of patients with an SVR was 52% (12/23). The percentage of genotype 1 patients with an SVR was 47% (7/15), and the percentage of genotype 2/3 patients with an SVR was 63% (5/8).

Conventional interferon/ribavirin combination therapy

Overall, 22% (36/167) of non-responders to prior interferon combination therapy had an SVR. For those with genotype 1

Table 2 Early virological response (EVR) and sustained virological response (SVR) following retreatment with peginterferon alfa-2a (40KD) plus ribavirin

	Peginterferon alfa-2a (40KD) + ribavirin		
	24 weeks (n = 28)	48 weeks (n = 284)	Total (n = 312)
EVR (n (%))*			
Non-responders	11/13 (84.6)	112/199 (56.3)	123/212 (58.0)
Relapsers	11/15 (73.3)	73/85 (85.9)	84/100 (84.0)
SVR (n (%))†			
Non-responders	5/13 (38.5)	43/199 (21.6)	48/212 (22.6)
Relapsers	8/15 (53.3)	33/85 (38.8)	41/100 (41.0)

*Decrease in hepatitis C virus (HCV) RNA ⩾2-log$_{10}$, or undetectable HCV RNA (<50 IU/ml) at week 12 of therapy.
†Negative HCV RNA (<50 IU/ml) at the end of 24 weeks of untreated follow up.

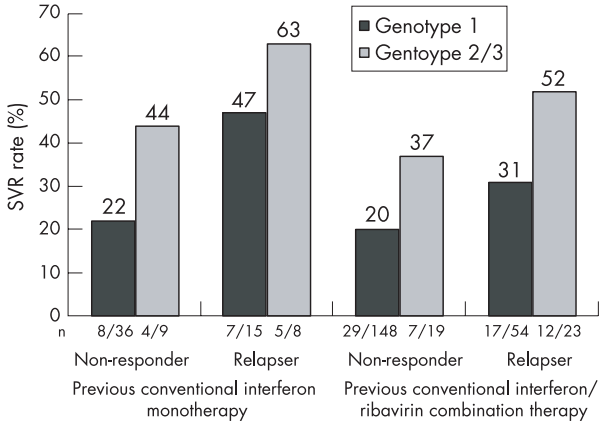

Figure 2 Sustained virological response (SVR) in non-responder and relapse groups by genotype.

infection, the SVR rate was 20% (29/148) and for genotype 2/3 infection it was 37% (7/19).

Of those who relapsed after previous combination therapy, the overall percentage of patients with an SVR was 38% (29/77). In genotype 1 patients, the SVR rate was 31% (17/54), and in genotype 2/3 patients, 52% (12/23) (fig 2).

Predictors of response to peginterferon alfa-2a (40KD) plus ribavirin

Efficacy data from each group were analysed separately in the logistic regression analysis. For relapser patients, HCV genotype ($p = 0.0178$), race (Caucasian *v* non-Caucasian; $p = 0.0225$) and HCV viral load ($p = 0.0005$) were significant predictors of SVR (table 3). For previous non-responders, sex ($p = 0.0107$), weight ($p = 0.0435$), BMI ($p = 0.0118$), fibrosis ($p = 0.0158$), and viral load ($p = 0.0113$) were significant predictors of SVR (table 3).

Predictability at week 12

There were too few genotype 2 or 3 patients to examine the predictability of a week 12 virological response. Data for patients infected with genotype 1 are shown in fig 3.

Non-responders to previous HCV therapy

Of the genotype 1 non-responders to previous HCV therapy (n = 184), EVR data were not available for six patients. Of the

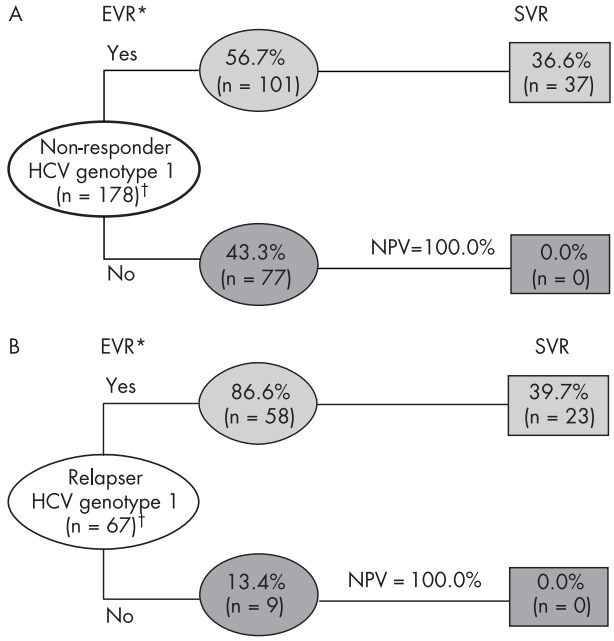

Figure 3 (A) Week 12 predictability in previous non-responders infected with hepatitis C virus (HCV) genotype 1. EVR, early virological response; NPV, negative predictive value; SVR, sustained virological response. *HCV RNA unquantifiable (<600 IU/ml) or drop of ≥2-$\log_{10}$ by polymerase chain reaction at week 12. †Six patients EVR unknown. (B) Week 12 predictability in previous relapsers infected with HCV genotype 1. *HCV RNA unquantifiable (<600 IU/ml) or drop of ≥2-$\log_{10}$ by polymerase chain reaction at week 12. †Two patients EVR unknown

remaining 178 patients, more than half (57%) had an EVR and 37% went on to have an SVR. Of the 77 patients without an EVR, none achieved an SVR (NPV = 100%) (fig 3A).

Relapsers to previous HCV therapy

Of those with HCV genotype 1, 87% achieved an EVR, and 40% had an SVR. For genotype 1 patients who failed to achieve EVR, the NPV for non-response was 100% (fig 3B).

The majority of genotype 1 infected patients who had an EVR (122 of 159 patients; comprising 51 relapsers and 71 non-responders) achieved a ≥2-$\log_{10}$ drop in HCV RNA at week 12 and were also below the limit of quantitation (HCV RNA <600 IU/ml). Of these, 52/122 went on to achieve an

Table 3 Logistic regression analysis of factors predictive of sustained virological response in relapsers and non-responders

Parameter	Odds ratio	95% CL		p Value
Relapsers (n = 94)				
Genotype (1 *v* 2 or 3)	0.263	0.087	0.793	0.0178
Age (y)	0.981	0.916	1.049	0.5723
Race (Caucasian *v* non-Caucasian)	0.098	0.013	0.720	0.0225
Sex (male *v* female)	0.704	0.178	2.779	0.6159
Weight (kg)	0.952	0.890	1.018	0.1482
BMI (kg/m^2)	1.053	0.865	1.282	0.6085
Fibrosis (F0, F1, F2 *v* F3, F4)	2.394	0.801	7.157	0.1181
Log HCV viral load	0.436	0.273	0.697	0.0005
Non-responders (n = 198)				
Genotype (1 *v* 2 or 3)	0.383	0.143	1.021	0.0551
Age (y)	0.973	0.926	1.022	0.2682
Race (Caucasian *v* non-Caucasian)	0.342	0.115	1.015	0.0533
Sex (male *v* female)	3.850	1.367	10.843	0.0107
Weight (kg)	1.058	1.002	1.117	0.0435
BMI (kg/m^2)	0.785	0.650	0.948	0.0118
Fibrosis (F0, F1, F2 *v* F3, F4)	2.513	1.189	5.311	0.0158
Log HCV viral load	0.670	0.492	0.913	0.0113

BMI, body mass index; HCV, hepatitis C virus; 95% CL, 95% confidence limits.

Table 4 Laboratory abnormalities and dose modifications

Abnormality (n (%))		Peginterferon alfa-2a (40KD) + ribavirin	
		24 weeks (n = 28)	48 weeks (n = 284)
Neutropenia*	Grade 3		
	Non-responders	2 (15.4)	37 (18.6)
	Relapsers	2 (13.3)	20 (23.5)
	Grade 4		
	Non-responders	0 (0%)	2 (1.0)
	Relapsers	0 (0%)	2 (2.4)
Dose modification for neutropenia†	Non-responders	2 (15.4)	37 (18.6)
	Relapsers	2 (13.3)	20 (23.5)
Thrombocytopenia‡	Grade 3		
	Non-responders	1 (7.7)	5 (2.5)
	Relapsers	0 (0.0)	6 (7.1)
Dose modification for thrombocytopenia†	Non-responders	1 (7.7)	11 (5.5)
	Relapsers	0 (0.0)	6 (7.1)
Anaemia§	Hb <10 g/dl		
	Non-responders	0 (0.0)	15 (7.5)
	Relapsers	1 (6.7)	9 (10.6)
Dose modification for anaemia¶	Non-responders	0 (0.0)	14 (7.0)
	Relapsers	1 (6.7)	9 (10.6)
ALT elevation**	Non-responders	0 (0.0)	4 (2.0)
	Relapsers	0 (0.0)	0 (0.0)
Dose modification for ALT elevation¶	Non-responders	0 (0.0)	3 (1.5)
	Relapsers	0 (0.0)	0 (0.0)

ALT, alanine aminotransferase; Hb, haemoglobin.
*Grade 3 neutropenia defined as an absolute neutrophil count of 500–700 cells/ml; grade 4 neutropenia defined as an absolute neutrophil count of <500 cells/ml.
†Deemed related to peginterferon alfa-2a (40KD).
‡Grade 3 thrombocytopenia defined as <50 000 platelets/ml.
§Anaemia defined as Hb <10 g/dl.
¶Deemed related to ribavirin.
**ALT elevation defined as a progressive increase in ALT over baseline values.

SVR (PPV = 43%). The numbers of patients who achieved a 2-$\log_{10}$ drop in HCV RNA, but remained above the limit of quantitation (>600 IU/ml; n = 19), and the number of patients whose HCV RNA was undetectable (<50 IU/ml; n = 10) were too small to allow any meaningful comparison of predictability using different criteria to be made.

Safety and tolerability

Twelve patients in the non-responder group (6%) and five patients in the relapser group (5%) prematurely withdrew from the study due to adverse events. The withdrawal rate due to adverse events in the 24 week group (3/28; 11%) was more than double that in the 48 week group (14/284; 5%) (fig 1).

The most frequent non-serious adverse events were neutropenia (24%), anaemia (9%), and thrombocytopenia (7%). Fifteen patients (5%) reported a total of 16 different serious adverse events. No difference in the frequency of serious or non-serious adverse events was seen between the non-responder and relapser groups.

Table 4 details laboratory abnormalities and resulting dose modifications. The incidences of neutropenia, thrombocytopenia, anaemia, and ALT elevations were higher in the 48 week treatment group than in the 24 week group. Neutropenia was the most common cause of dose modifications (14−20% of patients).

Early withdrawal from the study

Premature withdrawals are shown for each treatment group in fig 1. In the prior non-responder group, 110 of 212 patients (52%) withdrew from the study early. In the relapser group, the withdrawal rate was lower (23/100 patients; 23%). The main reason for early withdrawal in both groups was non-response to study medication (80/212 (38%) of non-responders and 11/100 (11%) relapsers). Although the study protocol recommended that patients who were HCV RNA positive at week 12 stop treatment, 71/93 patients without an EVR at week 12 were maintained on therapy at the discretion of the investigator or at the insistence of the patient.

DISCUSSION

At present there are limited data available on the efficacy of retreating previous treatment failures with pegylated interferon plus ribavirin. Here we report SVR data for previous treatment failures who were retreated with peginterferon alfa-2a (40KD) plus ribavirin. This relatively large cohort of patients underwent treatment as part of standard clinical care. We defined previous treatment failure as either non-response or relapse. In non-responders, patients were positive for HCV RNA at all times during previous therapy. There is some uncertainty in this definition because the frequency of HCV RNA testing during the previous course of therapy was not specified, and it is possible that HCV RNA could have been transiently below the limit of quantitation. Relapsers were defined as those who initially responded to therapy by clearing virus from serum, only to become HCV RNA positive once more, either during treatment or after treatment was complete. This definition also includes patients with ''breakthrough'' viraemia during treatment.

Several studies presented as abstracts have reported that the percentage of patients achieving an SVR when retreated with peginterferon plus ribavirin varies from 10% to 20%.[18–21] In the first reported study in this population to date, which was conducted exclusively in non-responder patients with advanced fibrosis/cirrhosis, 18% of patients reported an SVR following retreatment with peginterferon alfa-2a (40KD) plus ribavirin.[14] Krawitt and colleagues[15] have recently reported their results in retreating patients who failed previous interferon based therapy with pegylated interferon alfa-2b plus ribavirin. Our results are similar to those reported by Krawitt and colleagues.[15] Direct comparisons are difficult because Krawitt *et al* did not stratify their results in the same manner as we did. For example, in their study, prior genotype 1 non-responders to any treatment had an

SVR of 17% whereas in our study non-responders to prior monotherapy had a 22% SVR rate, and non-responders to prior combination therapy had an SVR rate of 20% with retreatment. Both studies showed that the response in genotypes 2 or 3 was better than in genotype 1, and that relapsers responded better than prior non-responders. Both studies also showed that patients who failed prior monotherapy did better than those who failed prior combination therapy. In our study, the SVR rate in those who failed conventional interferon monotherapy was 35%, and in those who failed conventional interferon/ribavirin combination therapy, 27%.

Since this study was conducted, it has been recognised that the optimal dose of ribavirin for patients infected with HCV genotype 1 is 1000/1200 mg/day dosed according to body weight, and that these patients should be treated for 48 weeks.[1 3] We used a ribavirin dose (800 mg/day) that would now be recognised as inadequate for genotype 1. Had all genotype 1 patients in our study been treated with the optimal ribavirin dose, the overall response rate would likely have been higher.

As expected, the SVR rate was higher in those who had relapsed during previous treatment (41%) than in those who were previous non-responders (23%), which both compare favourably with the SVR rate reported by Shiffman and colleagues[14] and Krawitt and colleagues.[15] Consistent with previous findings,[2–4] patients with HCV genotype 2 or 3 infection showed a higher SVR rate (48%) than those infected with genotype 1 (24%). In this study, the percentage of genotype 1 infected relapsers who had an SVR was 35% compared with 46−51% reported in treatment naïve patients in the large registration studies using an optimal dose of ribavirin.[2–4] For genotype 2/3 relapsers, our study found an SVR rate of 55% compared with a previously reported rate of 76–78% for treatment naive patients.[2–4] Unfortunately, the relatively small number of patients with HCV genotype 2 or 3 in this study (n = 59) meant it was not possible to make a meaningful comparison of the response rates between the two genotypes, or to accurately assess whether retreatment for 48 weeks produces better response rates than retreatment for 24 weeks.

In clinical trials of peginterferon plus ribavirin combination therapy, absence of an EVR at week 12 has been shown to have a high NPV for the probability of achieving an SVR.[2 22 23] In the study of peginterferon alfa-2a (40KD) plus ribavirin by Fried *et al*, 97% of those who did not have an EVR failed to achieve an SVR, and 65% of patients with an EVR subsequently achieved an SVR.[2] Due to the sensitivity of this assessment, EVR has become widely used in clinical practice to identify patients who are unlikely to respond to ongoing therapy. Early discontinuation of treatment can be considered in these patients because the likelihood of a long term response is so poor. Our study confirms that lack of an EVR is an accurate predictor of non-response, as no patient who failed to achieve an EVR subsequently went on to achieve an SVR (overall NPV = 100%). Thus, the week 12 ''decision point'' is also valid in retreatment of previous non-responders and relapsers.

Our study was conducted in a combined academic/community setting and was intended to be reflective of practice conditions in most communities. Although there is a perception that it may be difficult to replicate the efficacy rates of randomised clinical trials in routine clinical practice, we were able to achieve a comparable SVR rate to Shiffman and colleagues.[14] Furthermore, the adverse event discontinuation rate in the present study was comparable with those seen in the large scale registration studies of peginterferon alfa-2a (40KD) plus ribavirin.[2 3] Withdrawals due to adverse events were more frequent among patients treated for 24 weeks compared with those treated for 48 weeks (11% *v* 5%). However, this is likely a statistical anomaly because of the small number of patients in the 24 week treatment group. Successful outcome of therapy in this study is likely related to the availability of expert nursing assistance within many of the centres, which may have contributed substantially to maintaining patients on therapy. All of the physicians participating in the study were highly experienced in the management of chronic hepatitis C. We believe that these factors were crucial in our ability to obtain such good results. In addition, using similar eligibility criteria as the pivotal trials of peginterferon alfa-2a (40KD)/ribavirin meant that potentially problematic patients such as those with decompensated cirrhosis or ongoing substance abuse were excluded. This may have further contributed to the good SVR rate in our study.

In the HALT-C study, 18% of previous non-responders retreated with peginterferon alfa-2a (40KD) plus ribavirin achieved an SVR.[14] This cohort was treated with ribavirin 1000/1200 mg/day but was also composed exclusively of patients with advanced fibrosis/cirrhosis. In contrast, in our study, 49% of patients had bridging fibrosis/cirrhosis. As the presence of advanced fibrosis and cirrhosis is independently associated with a decreased SVR rate,[24 25] the lower proportion of such patients included in our study may explain why our results appear better than those of Shiffman and colleagues,[14] despite the suboptimal dose of ribavirin used in genotype 1 patients in our study.

In conclusion, the results obtained using peginterferon alfa-2a (40KD) plus ribavirin suggest that there is merit in retreating patients who failed either conventional interferon monotherapy or conventional interferon plus ribavirin combination therapy, and that acceptable response rates can be achieved in clinical practice. Even in the most refractory patient group, genotype 1 non-responders to interferon plus ribavirin, an SVR rate of 20% was obtained. The overall response rates of 23% for non-responders and 41% for relapsers may be improved further by using the optimal dose of ribavirin according to genotype. In the future, retreatment of previous non-responders to all interferon based therapies, including pegylated interferon/ribavirin combination therapy, will continue to be an important focus of clinical trials, and future studies should aim to address how we may optimise the therapeutic response to retreatment in this important group of patients.

ACKNOWLEDGEMENTS

The other contributing members of the Canadian Pegasys Study Group were:
Robert Bailey, Royal Alexandra Hospital, Edmonton, Alberta, Canada; Victor Feinman, Mount Sinai Hospital, Toronto, Ontario, Canada; Susan Greenbloom, Toronto Digestive Disease Associates Inc., Toronto, Ontario; Jenny Heathcote, University Health Network, Toronto Western Hospital, Toronto, Ontario, Canada; Nir Hilzenrat, Montreal Jewish General Hospital, Montreal, Quebec, Canada; Paul Marotta, London Health Sciences Centre Research, London, Ontario, Canada; Linda Scully, The Ottawa Hospital, Civic Campus, Ottawa, Ontario, Canada; Bernard Willems, CHUM-Hôpital Saint-Luc, Montreal, Quebec, Canada; Helga Witt-Sullivan, Hamilton Health Sciences Corp. General Site, Hamilton, Ontario, Canada; Lawrence Worobetz, Royal University Hospital, Saskatoon, Saskatchewan, Canada.
We thank Amanda Yu and Rohinish Gunadasa, Syreon Corporation, British Columbia, Canada, for statistical analysis and logistical support, and Trisha Hutzul, Roche Mississauga, Ontario, Canada for help with logistical issues in the early phases of the study.

Conflict of interest: declared (the declaration can be viewed on the *Gut* website at http://www.gutjnl.com/supplemental).

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The design, collection, analysis, and interpretation of data in the Canadian extended access program, as well as the resulting manuscript, were supported by a grant from Roche Canada.

Conflict of interest: None declared.

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